Degradation Kinetics on the Next Level

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Main Conclusion:

Simultaneous evaluation of all datasets obtained in the same environmental medium has the potential to yield more realistic endpoints in less time.

Overview

- Current guidance
- Simultaneous evaluations
- Tests with synthetic data
- Tests with observed data
- Conclusions

Current Guidance

Critical points regarding the FOCUS degradation kinetic guidance

Workload:
Model selection required for every dataset, and for several regulatory purposes

Ambiguities:
Expert judgement required for model selection, outcome often unpredictable

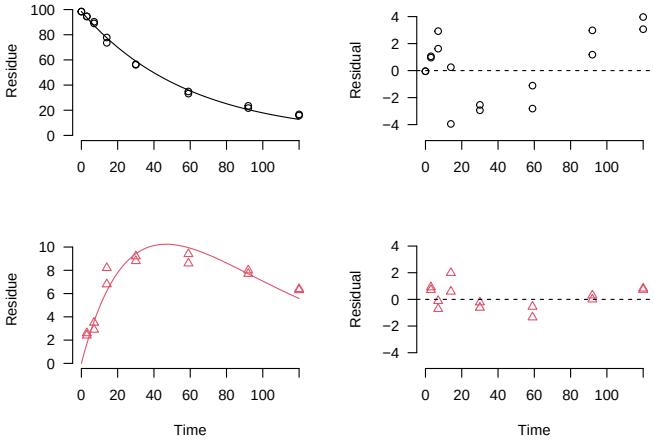
Scientific Basis:
The default half-life of 1000 days is arbitrary

State of the Art: Generalised Nonlinear Regression

Degradation Model:
SFO-SFO

Error Model:
Constant variance

Method:
Least squares



Soil Dataset 3 from Ranke and Meinecke (2019) *Environments* **6**(12) 124; R package mkin

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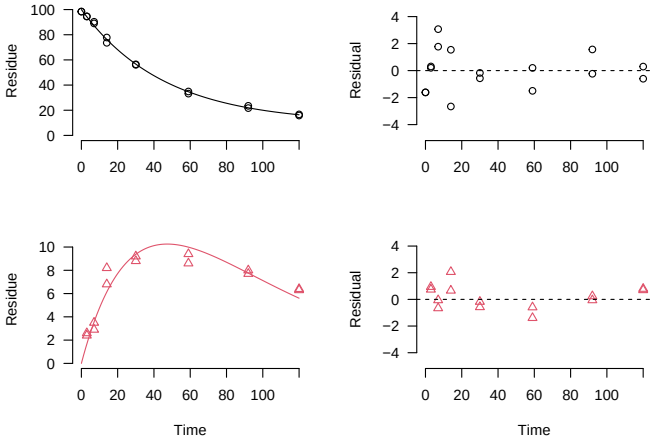


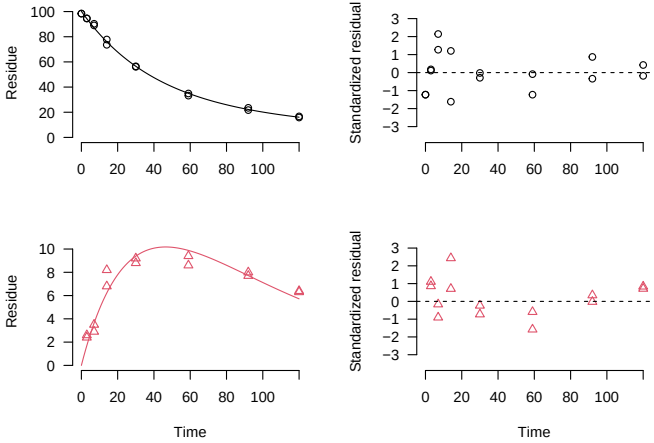
Soil Dataset 3 from Ranke and Meinecke (2019) *Environments* **6**(12) 124; R package mkin

State of the Art: Generalised Nonlinear Regression

Degradation Model:
DFOP-SFO

Error Model:
Variance by variable

Method:
Iterative reweighting (IRLS)



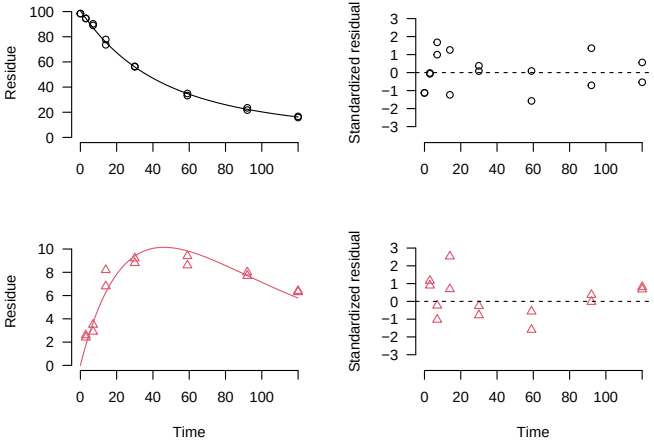
Soil Dataset 3 from Ranke and Meinecke (2019) *Environments* **6**(12) 124; R package mkin

State of the Art: Generalised Nonlinear Regression

Degradation Model:
DFOP-SFO

Error Model:
Two-component

Method:
Likelihood maximisation



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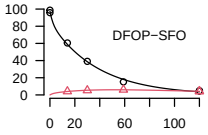
Separate Evaluations



$\rightarrow n_{0,1}, k_{1,1}, k_{2,1}, \ldots$

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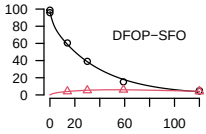

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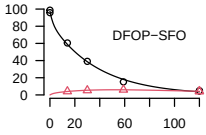
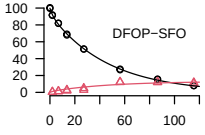
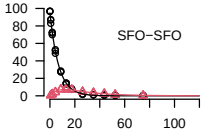


$\rightarrow n_{0,1}, k_{1,1}, k_{2,1}, ...$



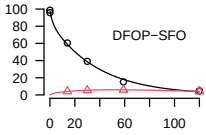
$\rightarrow n_{0,2}, k_{1,2}, k_{2,2}, ...$



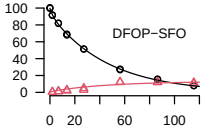
$\rightarrow n_{0,3}, k_3, ...$

R package mkin

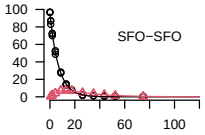
Separate Evaluations



$\rightarrow n_{0,1}, k_{1,1}, k_{2,1}, ...$



$\rightarrow n_{0,2}, k_{1,2}, k_{2,2}, ...$



$\rightarrow n_{0,3}, k_3, ...$

$\rightarrow$ Geometric mean k
Mean formation fractions

R package mkin

The Next Level: Parameter Distribution Model

Already Used:
Normal distribution of log rate constants

EFSA (2014) EFSA Guidance Document for evaluating laboratory and field dissipation ...

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The Next Level: Parameter Distribution Model

Already Used:
Normal distribution of log rate constants

Generalised Assumption:
Suitably transformed degradation model parameters follow a normal distribution

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Normal distribution of log rate constants

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Well-established Method:
Nonlinear mixed-effects models for grouped data

Pinheiro and Bates (2000), Lavielle (2015)

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Already Used:
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Generalised Assumption:
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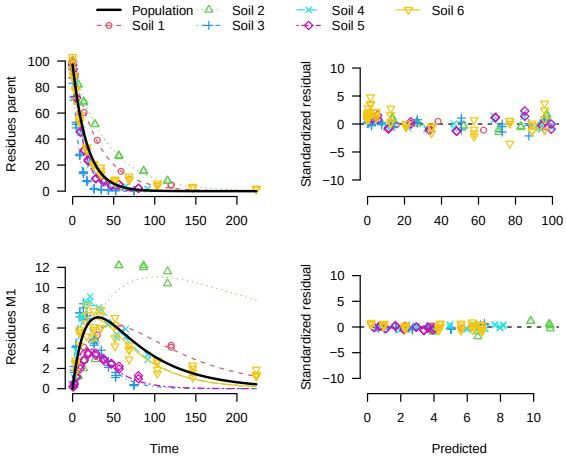
Well-established Method:
Nonlinear mixed-effects models for grouped data
Also known as hierarchical models or multilevel models

Simultaneous Evaluations: Nonlinear Mixed-Effects Models



Degradation Model:
SFO-SFO

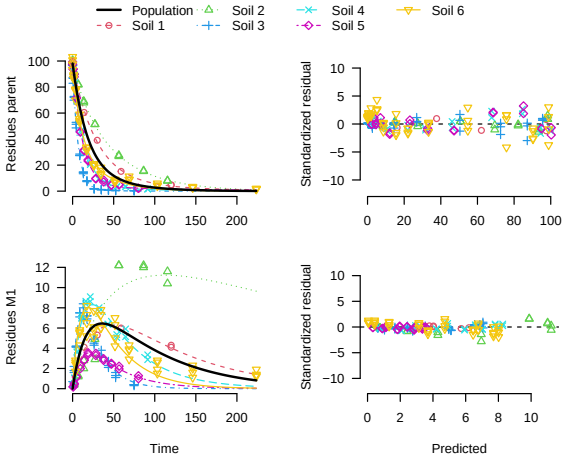
Parameter Model:
Uncorrelated normal distribution

Error Model:
Constant variance

AIC: 1333.9 BIC: 1332.0

R packages mkin and saemix; Comets *et al.* (2017)

Simultaneous Evaluations: Nonlinear Mixed-Effects Models



Degradation Model:
DFOP-SFO

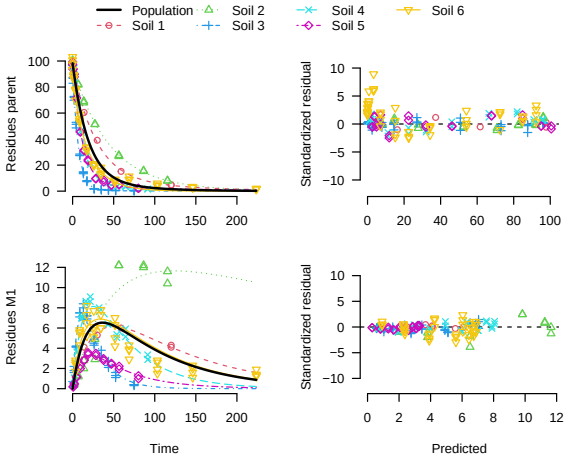
Parameter Model:
Uncorrelated normal distribution

Error Model:
Constant variance

AIC: 1185.8 BIC: 1183.1

R packages mkin and saemix; Comets *et al.* (2017)

Simultaneous Evaluations: Nonlinear Mixed-Effects Models



Degradation Model:
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Parameter Model:
Uncorrelated normal distribution

Error Model:
Two-component

AIC: 1085.3 BIC: 1082.4

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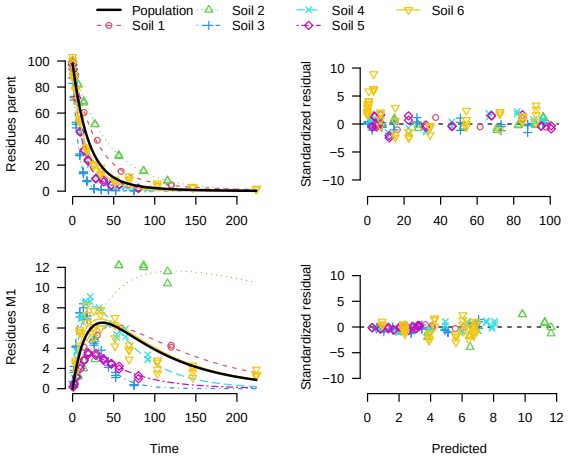
Simultaneous Evaluations: Nonlinear Mixed-Effects Models



Degradation Model:
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→ Most likely population parameters with estimated distributions

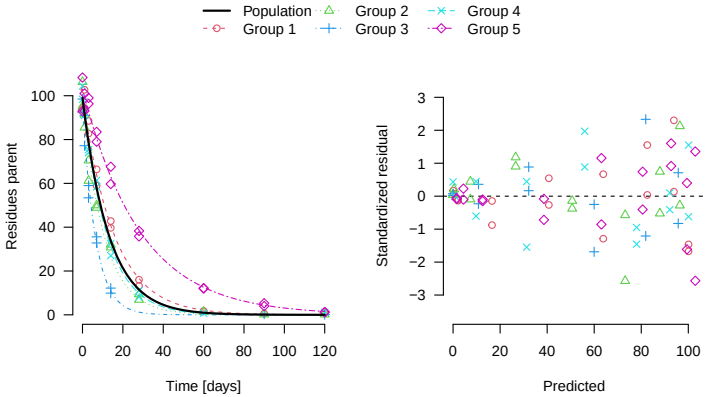
R packages mkin and saemix; Comets *et al.* (2017)

Recovery of Half-lives from Synthetic Data

Data Generation:
5 half-lives from normal distribution
Two-component error

Mean DT_{50} **15 days**

Evaluation:
Separate fits
Constant variance



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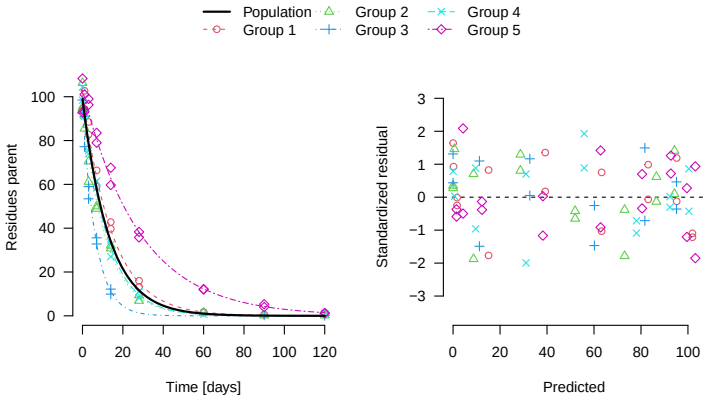

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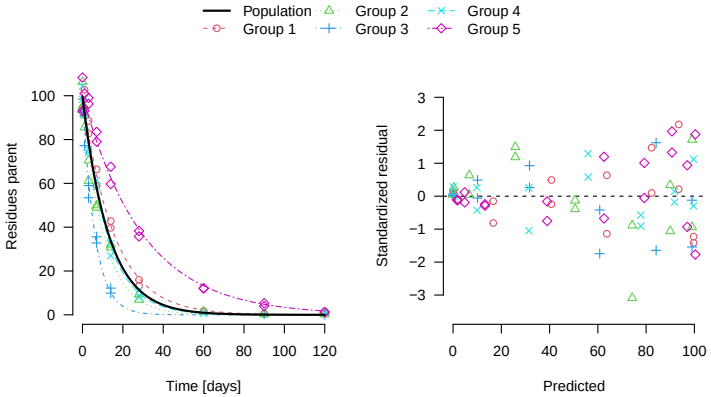

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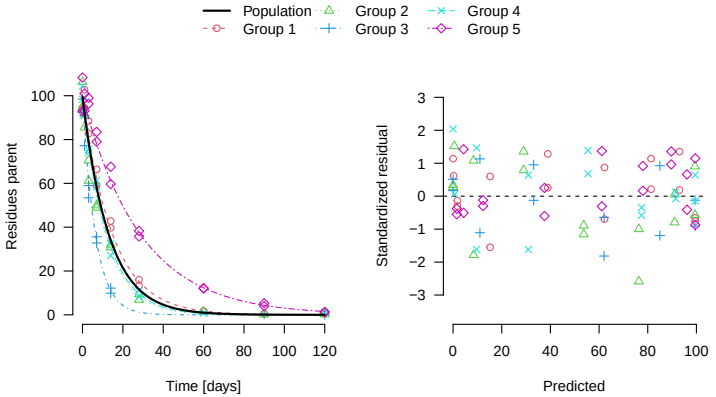

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Recovery of Half-lives from Synthetic Data

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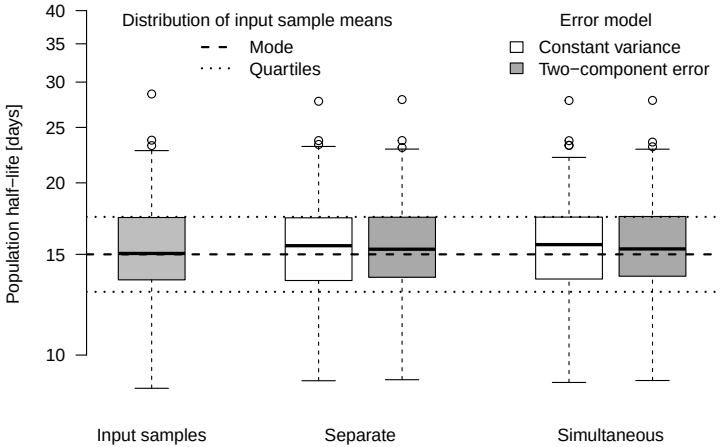
Mean DT_{50} **15 days**

100 x 5 datasets



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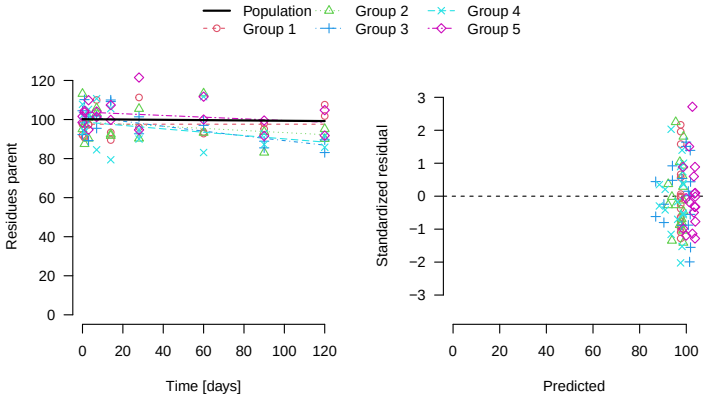
Umwelt Bundesamt

Recovery of Half-lives from Synthetic Data

Data Generation:
5 half-lives from normal distribution
Two-component error

Mean DT_{50} **800 days**

Evaluation:
Separate fits
Constant variance



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Umwelt Bundesamt

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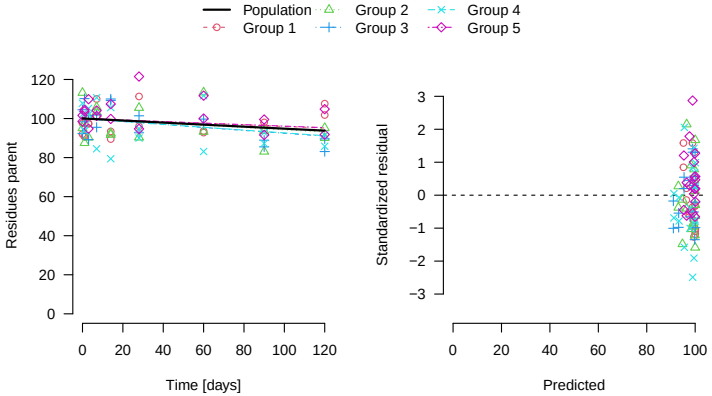

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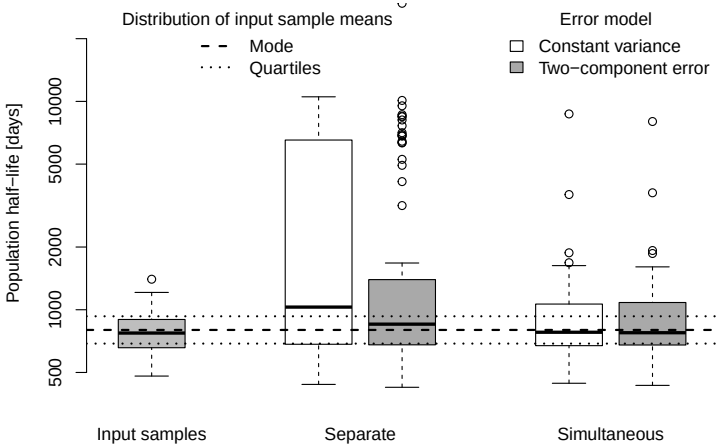

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Recovery of Other Parameters from Synthetic Data

Data Generation:
8 parameter sets from normal distributions of transformed parameters
Two-component error

Evaluation:
Separate fits
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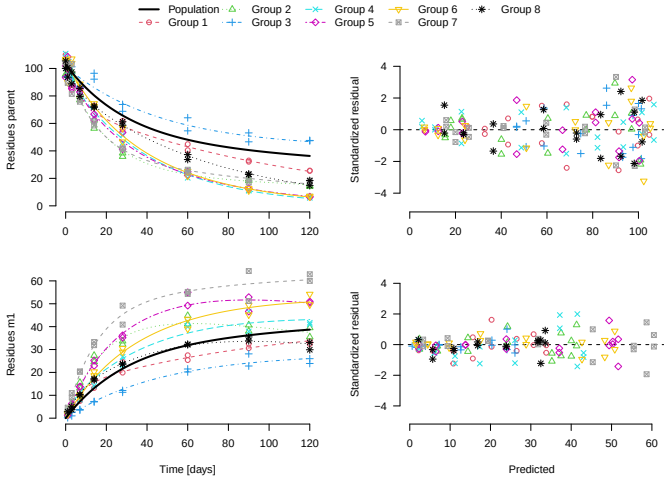

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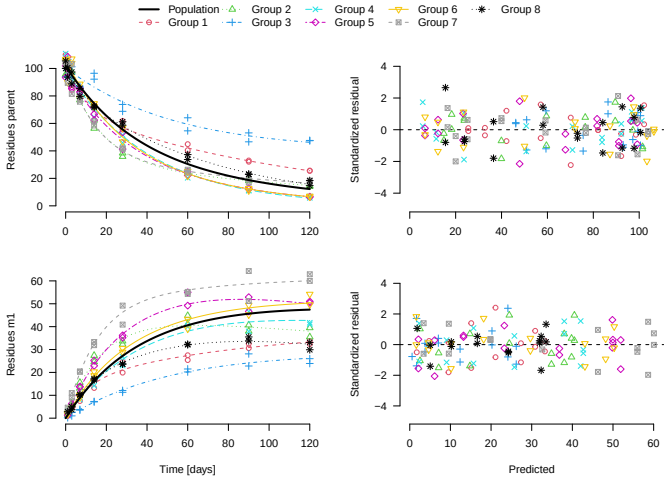

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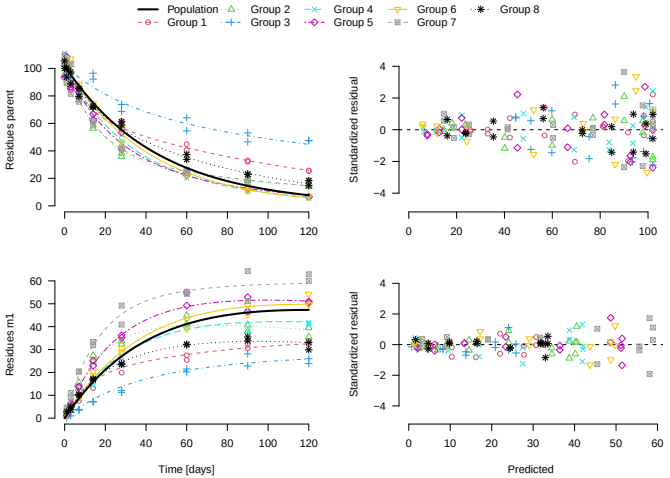

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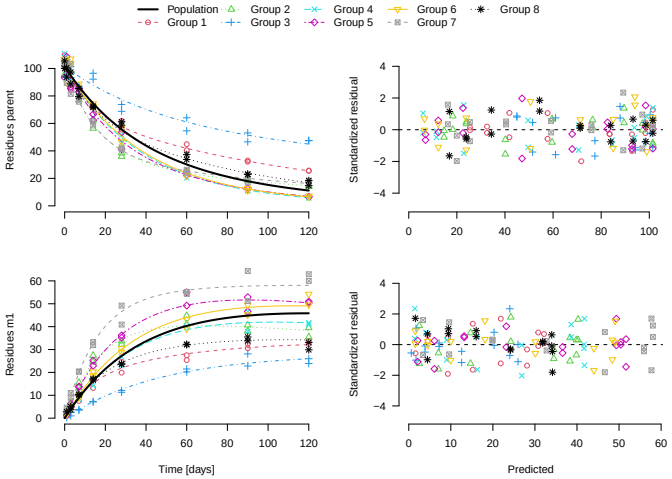

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Recovery of Other Parameters from Synthetic Data

Data Generation:
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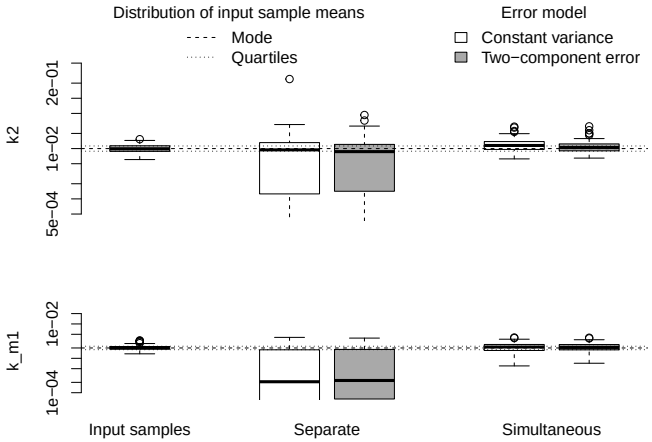
Two-component error

100 x 5 datasets

Critical parameters:
Slow rate constant parent
Metabolite rate constant



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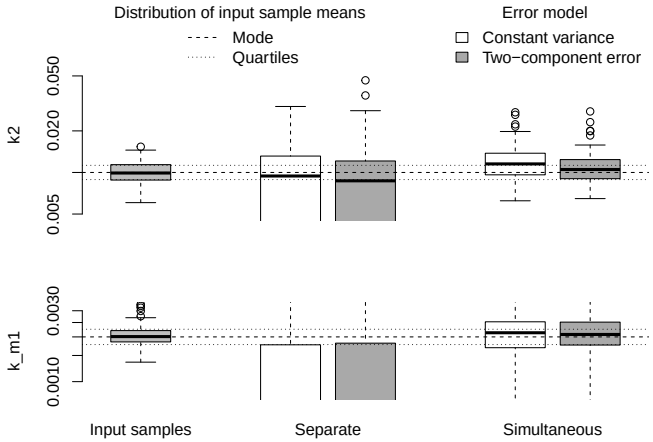

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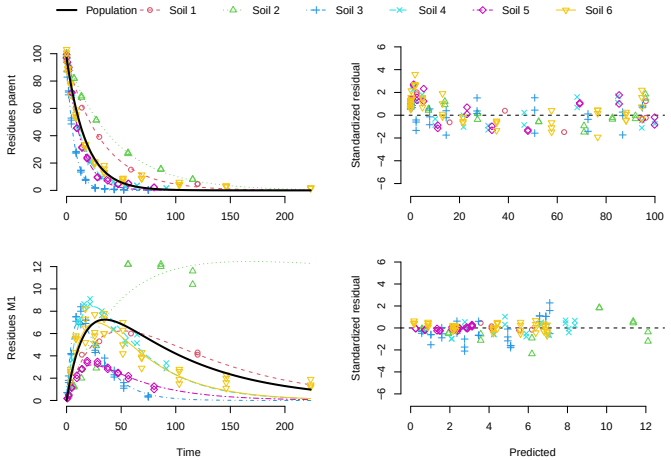
Observed Data: Separate Evaluations

Population Curve:
Mean values of transformed best-fit parameters



Data from RAR (2017)
R package mkin

Observed Data: Separate Evaluations

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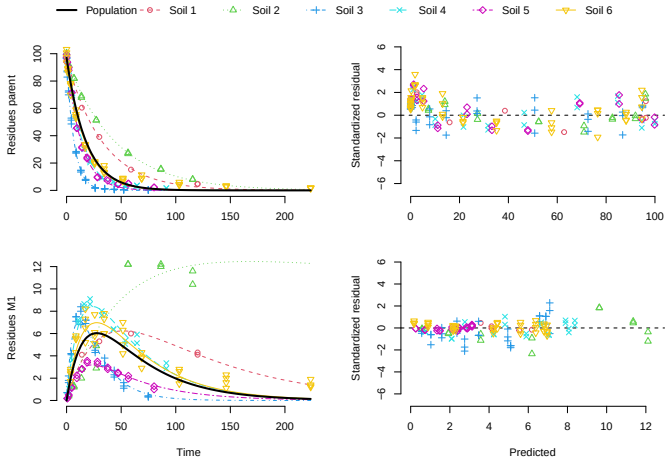
Only significant rate constants ($p \leq 0.10$)



Data from RAR (2017)
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Observed Data: Separate Evaluations

Population Curve:
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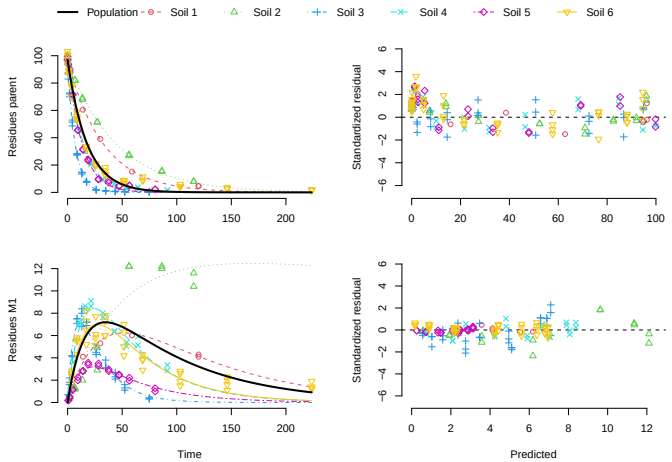
Use default half-life of 1000 days for non-significant rate constant (Soil 2)



Data from RAR (2017)
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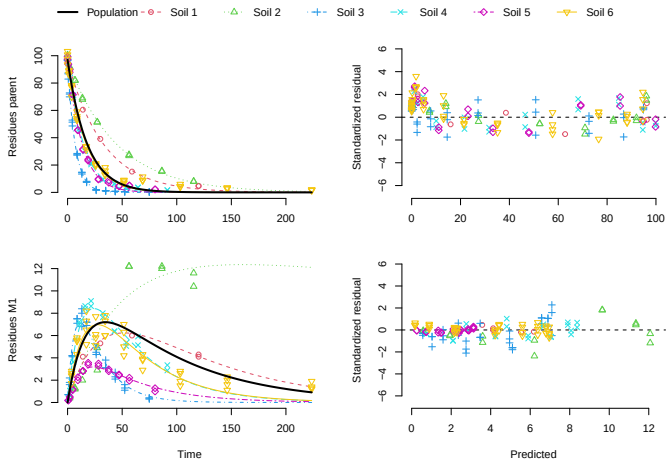
Observed Data: Separate Evaluations

Population Curve:
Mean values of transformed best-fit parameters

Only significant rate constants ($p \leq 0.10$)

Use default half-life of 1000 days for non-significant rate constant (Soil 2)
and update the formation fraction



Data from RAR (2017)
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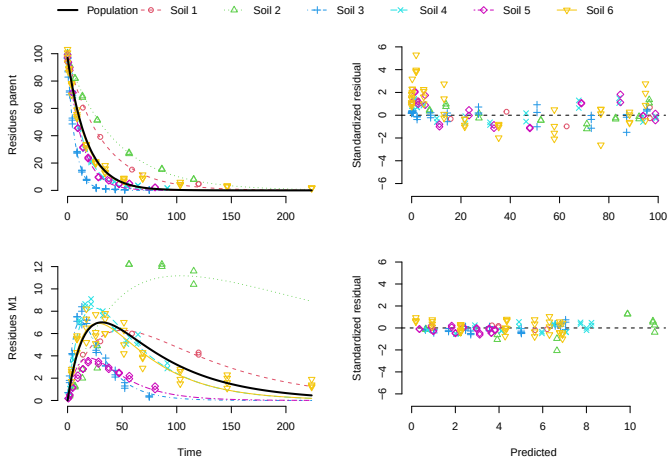
Observed Data: Simultaneous Evaluation

Population Curve:
Most likely population parameters from nonlinear mixed-effects model

- No data ignored



Data from RAR (2017)
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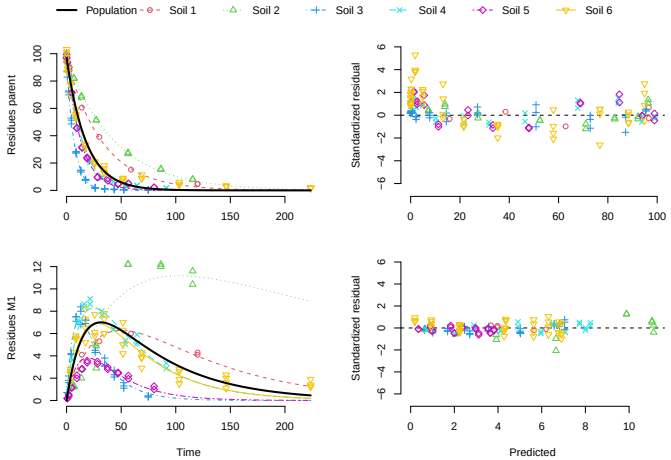
Observed Data: Simultaneous Evaluation

Population Curve:
Most likely population parameters from nonlinear mixed-effects model

- No data ignored
- No arbitrary defaults



Data from RAR (2017)
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Conclusions

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- Model selection only required for the complete data set

Next Steps:

→ Some technical and usability improvements are desirable

→ More case studies

Acknowledgements

Stefan Meinecke, Jana Schmidt, Thomas Gräff
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Emmanuelle Comets
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Univ Rennes, INSERM, EHESP, Irset